

REMARKS

Reconsideration of the application in view of the above amendments and following remarks is respectfully requested.

Claims 66-77 were pending in the subject application. Claim 66 has been amended to increase the clarity of the claimed invention. Support for the language is found, for example, at page 11, lines 2-10, and claim 73 of the subject application. Claims 67 and 70 have been amended for consistency with amended claim 66. Claim 73 has been cancelled without prejudice in view of the amendment to claim 66. Claims 74-75 have been amended to change their dependency in view of the cancellation of claim 73. No new matter has been added. Therefore, amended claims 66-72 and 74-77 are now pending.

In the Office Action dated October 1, 2002, claims 66-77 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. This rejection is respectfully traversed.

Applicants respectfully submit that the pending claims as originally filed were sufficiently definite to satisfy Section 112, second paragraph. Nevertheless, in order to increase the clarity, claim 66 (and thus pending claims 67-72 and 74-77 which depend therefrom) has been amended. The terms "accessible" and "capable of" have been deleted, and language added to specify the modification to annexin. Accordingly, the language objected to by the Examiner has been addressed.

Therefore, Applicants believe that the rejection of claims 66-77 under 35 U.S.C. § 112, second paragraph, has been overcome. Withdrawal of this objection is respectfully requested.

In the Office Action, claims 66-75 were rejected to under 35 U.S.C. § 102(b) as unpatentable over Tait et al. (WO 92/19279). Applicants respectfully traverse this rejection.

The Examiner points to Tait et al. as disclosing native annexin radiolabeled directly with <sup>125</sup>I. As set forth above, claim 66 has been amended to enhance the clarity of the claimed invention. Regardless of the Examiner's interpretation of claim 66 as filed, amended claim 66 does not encompass a native annexin. Further, amended claim 66 recites that a metal radionuclide is complexed directly to the annexin. Tait does not teach radiolabeling of annexin

with a metal radionuclide. Accordingly, amended claim 66 (and thus claims 67-72 and 74-77 which depend therefrom) is not anticipated by Tait et al.

Therefore, Applicants believe that the rejection of claims 66-77 under 35 U.S.C. § 102(b) has been overcome. Withdrawal of this rejection is respectfully requested.

In the Office Action, claims 66-77 were rejected under 35 U.S.C. § 103(a) as unpatentable over Tait et al. (WO 92/19279) in view of Reutelingsperger (U.S. Patent No. 5,627,036) or Theodore et al. (U.S. Patent No. 5,578,287). This rejection is respectfully traversed.

At page 4 of the Office Action, it is asserted that "Tait discloses a modified annexin V which is radiolabeled with  $^{125}\text{I}$  at a -SH group, as set forth above" [referring to page 3 of the Office Action]. At page 3 of the Office Action, it is asserted that "Tait specifically discloses radiolabeled annexin V, i.e.,  $^{125}\text{I}$ -annexin V, which is complexed with the radionuclide at a sulphydryl group (-SH) of the third Cys residue (e.g., thus is a modified annexin, annexin V-N1, see examples I and XVII." At page 4 of the Office Action, it is asserted that it "would have been obvious to one of ordinary skill in the art to modify the  $^{125}\text{I}$  labeled annexins disclosed by Tait by substituting the  $^{125}\text{I}$  for  $^{99\text{m}}\text{Tc}$  ...." Applicants respectfully disagree with all these assertions.

Applicants respectfully submit that the Patent Office has not established a *prima facie* case for obviousness of the claimed invention under Section 103(a). Contrary to the Office Action, the  $^{125}\text{I}$  label in Tait et al. is not complexed with a sulphydryl group, such as on the Cys residue of annexin V-N1. Instead, the  $^{125}\text{I}$  is attached to a Tyr and/or His residue, and does not involve a sulphydryl group as neither of these amino acids contains a sulfur atom. In Example I of Tait et al., iodinated annexin V is prepared using the Iodogen reagent (page 27, lines 16-18, of Tait et al.). Submitted herewith are two documents describing iodination using Iodogen reagent (IODO-GEN®). In the document by Pierce Chemical, the structure of the reagent is depicted and its use is discussed. In the document by Amersham Biosciences, it is stated that radioiodination of proteins and peptides in the presence of an oxidizing agent such as Iodogen, results in the labeling of Tyr (tyrosine) or His (histidine) amino acid residues. Nowhere in these documents is it taught that Cys (cysteine) is radioiodinated by using Iodogen. Therefore, the  $^{125}\text{I}$  label in Tait et al. (e.g., Example I) is not complexed with a sulphydryl group of annexin or annexin V-N1.

As noted above, the Office Action also draws Applicants' attention to Example XVII of Tait et al. (pages 46-48). Example XVII refers to the design of an amino-terminally extended annexin ("annexin V-N1") which is connected to the amino-terminal Ala residue of mature annexin V. It is stated (page 46, lines 22-23 of Tait et al.) that the "SH group of the third Cys residue may be used for conjugates with iodoacetyl-scuPA." (As described at page 34, lines 11-12 of Tait et al., "scuPA" is human single-chain urokinase-type plasminogen activator.) Thus, the SH group is added so as to conjugate a protein (scuPA) and not to participate in the complexation of a metal radionuclide. Accordingly, contrary to the Office Action, Tait et al. does not disclose radiolabeled annexin V which is complexed with the radionuclide at a sulfhydryl group (-SH) of the third Cys residue of annexin V-N1.

Therefore, contrary to the conclusion of the Section 103 (a) rejection as set forth at page 4 of the Office Action, it would not have been obvious to one of ordinary skill in the art at the time of Applicants' invention to modify  $^{125}\text{I}$ -labeled annexins of Tait et al. (which are not labeled at a sulfhydryl group) by substituting the  $^{125}\text{I}$  with  $^{99\text{m}}\text{Tc}$ .

Applicants respectfully, but strenuously, submit that the Patent Office has not met the burden of establishing a *prima facie* case for obviousness of the claimed invention.

Therefore, Applicants believe that the rejection of claims 66-77 under 35 U.S.C. § 103(a), has been overcome. Withdrawal of this rejection is respectfully requested.

Therefore, in light of the amendments and remarks set forth above, Applicants believe all the Examiner's rejections have been overcome. Consideration of the references submitted herewith, and reconsideration and allowance of the pending claims (66-72 and 74-77) are respectfully requested.

If there is any further matter requiring attention prior to allowance of the subject application, the Examiner is respectfully requested to contact the undersigned attorney (at 206-622-4900) to resolve the matter.



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PATENT TRADEMARK OFFICE

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

A handwritten signature in black ink, appearing to read "Richard G. Sharkey", written over a horizontal line.

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Enclosures:

Excerpt from Pierce Chemical

Excerpt from Amersham Biosciences